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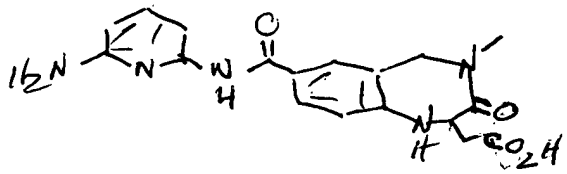
(54) Title: COMPOSITIONS AND METHODS FOR INHIBITING CLOT FORMATION

(57) Abstract

A pharmaceutical composition comprising a glycoprotein IIb/IIIa receptor antagonist and an $\alpha_v\beta_3$ receptor antagonist. The invention is also a method for reducing the risk of acute coronary ischemic syndrome in patients at risk to acute coronary ischemic syndrome comprising administering to the patient a safe and effective amount of a glycoprotein IIb/IIIa receptor antagonist and a safe and effective amount of an $\alpha_v\beta_3$ receptor antagonist.



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TITLE OF THE INVENTION

COMPOSITIONS AND METHODS FOR INHIBITING CLOT FORMATION

BACKGROUND OF THE INVENTION

Platelet activation and aggregation are involved in unstable angina and acute myocardial infarction, in reocclusion following thrombolytic therapy and angioplasty, in transient ischemic attacks and in a variety of other vaso-occlusive disorders. When a blood vessel is damaged either by acute intervention such as angioplasty, or, more chronically, by the pathophysiological processes of atherosclerosis, platelets are activated to adhere to the disrupted surface and to each other. This activation, adherence and aggregation may lead to occlusive thrombus formation in the lumen of the blood vessel.

Antiplatelet therapy has been used in a wide variety of cardiovascular disease states and in conjunction with interventional therapy such as coronary artery or peripheral bypass grafting, cardiac valve replacement, and percutaneous transluminal coronary angioplasty (PTCA). Available drugs, such as aspirin and ticlopidine, have shown efficacy in syndromes involving vascular occlusion, presumably due to sustained inhibition of platelet function. However, the inhibitory effects of aspirin and ticlopidine are dependent upon the agonist which activates the platelet. For example, aspirin is effective in blocking platelet aggregation induced by agonists such as collagen that are dependent upon the cylooxygenase pathway. It is, however, less effective against concentrations of thrombin which can act by cyclooxygenase independent pathways. Likewise, ticlopidine's inhibitory effects can be overcome by combinations of agonists. Thus, an efficacious inhibitor of platelet aggregation that acts independently of the agonist and the pathway activating the platelet could be an important therapeutic advance giving greater efficacy than aspirin or ticlopidine in a broader spectrum of thrombotic events.

Integrin Superfamily

The firm attachment of endothelial cells to the subendothelial extracellular matrix is mediated via CAMs, which serve as receptors recognizing an array of adhesive proteins in the extracellular matrix. These proteins include von Willebrand factor (vWf), fibronectin, vitronectin, thrombospondin, laminins, collagen fibrils, elastin, microfibrils of elastin, and glycosaminoglycans. Most of the matrix adhesive molecules are the ligands for integrin receptors expressed in endothelial cells.

Integrins constitute an extended family ("superfamily") of membrane receptors interacting with adhesive proteins in plasma and extracellular matrix and with other membrane receptors (counter-receptors). The name "integrin" implies that they integrate the ligands on the outside of the cell with the cytoskeletal apparatus in the inside of the cell. Integrin receptors consist of a noncovalently lined Ca^{2+}-dependent, heterodimeric glycoprotein complex composed of α and β subunits. The eight known integrin β subunits give rise to eight families in which one "founder" β subunit forms heterodimers with different α subunits. There are at least 14 known α subunits. Among them α_V ("v" stands for association with the vitronectin receptor) seems to be most promiscuous, forming liaisons with six different β subunits. Receptors belonging to the β_1 and β_3 families are expressed in endothelial cells. The β_1 family, also named Very Late Antigens (VLA), is represented by the fibronectin receptor ($\alpha_5\beta_1$, or VLA-5), the collagen receptor ($\alpha_2\beta_1$, or VLA-2) and the laminin receptor ($\alpha_6\beta_1$). The β_3 family is represented by the vitronectin receptor ($\alpha_V\beta_3$), which is structurally similar (the same β_3 subunit) to the platelet integrin receptor for fibrinogen, glycoprotein IIb-IIIa complex ($\alpha_{IIb}\beta_3$). The functional difference between these two receptors is that the platelet receptor recognizes the γ chain domain (HHLGGAKQAGDV) of human fibrinogen and the endothelial vitronectin receptor does not. Both recognize the sequence R-G-D identified as the cell adhesion site of fibronectin, vitronectin, vWf, and the α chain of human fibrinogen. Therefore, synthetic peptides

containing the R-G-D sequence cause detachment of endothelial cells from the extracellular in matrix *in vitro*.

Vitronectin (serum spreading factor or S protein) is a 75-kDa glycoprotein found in plasma (500 μg/mL) and in extracellular matrix, including endothelial cell subendothelium (Barnes et al. J. Biol. Chem. 258; 12548 (1983); Hayman et al. Proc. Natl. Acad. Sci. USA 80; 4003, (1983); and Preissner et al. Blood 71; 1381 (1986)). Endothelial cells express a surface receptor for vitronectin ($\alpha_v\beta_3$) and bind vitronectin (Fitzgerald et al. Biochemistry 26: 8158 (1987); Cheresh et al. Proc. Natl. Acad. Sci. USA 84; 6471 (1989); Cheng et al. J. Cell Physiol. 139; 275 (1989); Preissner et al. ibid.; and Polack et al. Blood 73; 1519 (1989)). Vitronectin mediates attachment and spreading of endothelial cells, the development of focal adhesion plaques, and clustering of the vitronectin receptor (Dejana et al. Blood 75; 1509 (1990); Dejana et al. J. Cell Biol. 107;1215 (1988); Dejana et al. Blood 71;566 (1988); Charo et al. J. Biol. Chem. 262;9935 (1987); Cheresh et al. Proc. Natl Acad. Sci. USA 84;6471, (1987); Cheng et al. J. Cell Physiol. 139;275 (1989); Barnes et al. J. Biol. Chem. 258:12548 (1983); Hayman et al. J. Cell Biol. 95;20 (1982)). Vitronectin is also found in platelets and is released when platelets are activated; vitronectin then binds to platelets, probably to GP IIb-IIIa (Barnes et al. Proc. Natl. Acad. Sci. USA 80;1362 (1983)). Vitronectin thus acts as a subendothelial attachment factor for both endothelial cells and platelets. Vitronectin also mediates the adherence of group A and G streptococci to endothelial cells.

GPIIb/IIIa Inhibitors

The final obligatory step in platelet aggregation is the binding of fibrinogen to an activated membrane-bound glycoprotein complex, GP IIb/IIIa ($\alpha_{II}\beta_3$). Platelet activators such as thrombin, collagen, epinephrine or ADP, are generated as an outgrowth of tissue damage. During activation, GP IIb/IIIa undergoes changes in conformation that results in exposure of occult binding sites for fibrinogen. There are six putative recognition sites within fibrinogen for GP IIb/IIIa and thus fibrinogen can potentially act as a hexavalent ligand

to crossing GP IIb/IIIa molecules on adjacent platelets. A deficiency in either fibrinogen or GP IIb/IIIa prevents normal platelet aggregation regardless of the agonist used to activate the platelets. Since the binding of fibrinogen to its platelet receptor is an obligatory component of normal aggregation, GP IIb/IIIa is an attractive target for an antithrombotic agent.

Results from clinical trials of GP IIa/IIIa inhibitors support this hypothesis. The monoclonal antibody 7E3, which blocks the GP IIb/IIIa receptor, has been shown to be an effective therapy for the high risk angioplasty population. It is used as an adjunct to percutaneous transluminal coronary angioplasty or atherectomy for the prevention of acute cardiac ischemic complications in patients at high risk for abrupt closure of the treated coronary vessel.

A study reported in The New England Journal of Medicine vol. 330, No. 14, pp. 956-961 (1994) showed a decrease from 12.8% to 8.3% in the combined endpoints of death, non-fatal MI and need for urgent revascularization with fibrinogen receptor blockade. This benefit was at the expense of some additional risk of bleeding, with the need for transfusion increasing from 3% to 6%, and the incidence of patients with decreased hematocrit increasing from 7% to 15%. 7E3 was added to the standard regime of heparin and aspirin thus leaving few hemostatic control mechanisms intact. The clinical benefits of this drug could be seen at 6 months.

Many other studies have shown that blocking the GPIIb/IIIa receptor will stop platelet aggregation induced by all of the agonists and thus prevent thrombus formation but leave platelet adhesion relatively intact. The 7E3 monoclonal antibody is described in Coller et al. Ann. NY Acad. Sci. 1991; 614: 193-213; and Coller et al. J. Clin Invest. 1985; 76: 101-108. Others have used agents based on the RGD sequence, including snake venom proteins, small peptides, and peptidomimetics (Cook et al. Drugs of Future 1994; 19: 135-159; and Cox et al. Medicinal Research Reviews 1994; 14: 195-228).

The snake venom proteins, termed disintegrins, have provided important structural information, but their antigenicity has

limited their development as therapeutic agents (Cook et al. ibid.; and Cox et al.ibid.). Integrelin is a cyclic peptide that is based on the KGD sequence in the snake venom protein barbourin (Cook et al. ibid.; and Cox et al. ibid.). It inhibits ligand binding to GPIIa/IIIa but has very little effect on ligand binding to $\alpha_v\beta_3$. Among the non-peptide compounds are Ro 44-9883 and MK-383, which are administered intravenously, and are also selective for GPIIb/IIIa (Cook et al. ibid.; and Cox et al. ibid.). Orally active agents include SC54684, which is a prodrug (i.e., it requires biotransformation *in vivo* to its active form) with high oral bioavailability and RO43-8857, GR144053, and DMP728, which are themselves the active inhibitors (Cook et al. ibid.; and Cox et al. ibid.). Literally thousands of other compounds have been synthesized in an attempt to obtain optimal potency, metabolic stability, receptor specificity, and favorable intravascular survival. Despite variations in these compounds, virtually of all of them retain the basic charge relations of the RGD sequence with a positive charge separated from a negative charge by approximately 10-20 Å (Cook et al. ibid.; and Cox et al. ibid.).

Platelet aggregation is profoundly inhibited when increasing concentrations of murine 7E3 or c7E3 Fab are added to platelet-rich plasma *in vitro* or administered in incremental doses to animals or humans *in vivo* (Coller et al. Ann. NY Acad. ibid.; Tcheng et al. ibid.; and Simoons et al. Circulation 1994; 89:596-603). There is an excellent correlation between the percentage of receptors blocked and the inhibition of aggregation, with nearly complete inhibition of aggregation when 80% or more of the receptors are blocked (Coller et al. Ann. NY Acad. ibid.).

The results of the 7E3 study support the hypothesis that blockade of GPIIb/IIIa receptors is more effective than aspirin in preventing platelet thrombi, even in the presence of heparin. They also support the hypothesis that platelet-dependent thrombi frequently contribute significantly to the development of ischemic complications after PTCA, even when minor mechanical dissections are present.

There are several potential mechanisms by which c7E3 Fab may product a decrease in clinical restenosis. Inhibiting GPIIb/IIIa

should lead to fewer platelets in a thrombus that can release PDGF, an agent thought to contribute to restenosis via effects on intimal hyperplasia. In addition, c7E3 Fab decreases platelet thrombus formation, producing less extensive mural thrombus. Since atherosclerosis may undergo rapid progression when the blood vessel incorporates mural thrombus into the wall, a reduction in mural thrombus may translate into decreased progression of the atherosclerotic process. Finally since thrombin itself has been implicated in accelerating intimal hyperplasia (Schwartz J. Clin. Invest. 1993; 91:4), the anticoagulant effect of c7E3 Fab may also contribute to this phenomenon.

7E3 not only blocks the GPIIb/IIIa receptor but also blocks the $\alpha_v\beta_3$ vitronectin receptor, raising the possibility that blockade of this receptor may also contribute to an effect on clinical restenosis. The 7E3 antibody began as an intact murine IgG (Coller et al. J. Clin. Invest. ibid.), but fragments missing the Fc region were used for *in vivo* studies so as to decrease the likelihood of rapid clearance of platelets via an Fc-mediated mechanism (Coller at al. Ann. NY Acad. ibid.). A recombinant chimeric Fab version of 7E3 (c7E3 Fab) containing the mouse variable regions and human constant regions (Tcheng et al. Circulation 1994; 90: 1757-1764) was prepared. All forms of 7E3 inhibit the $\alpha_v\beta_3$ vitronectin receptor as well as GPIIb/IIIa (Coller et al. Blood 1991; 77:75-83; and Coller et al. Ann. NY Acad. ibid.).

Since $\alpha_v\beta_3$ is on platelets, endothelial cells, and perhaps smooth muscle cells (Felding-Habermann et al. Curr. Opin. Cell Biol. 1993; 5:864-868), there are many potential sites of action. Recently Choi *et al.* demonstrated that a peptide that blocks $\alpha_v\beta_3$ prevented intimal hyperplasia after vascular injury in the rat (Choi et al. J. Vasc. Surg. 1994; 19:125-134), and Matsuno *et al.* demonstrated that a peptide that reacts with GPIIIb/IIIa and $\alpha_v\beta_3$ prevents neointima formation in the hamster (Matsuno et al. Circulation 1994; 90:2203-2206). Whether the peptide used by Choi *et al.* also inhibited rat platelet GPIIb/IIIa is not known.

Although the monoclonal antibody 7E3 is known to block the IIb/IIIa receptor and the $\alpha_v\beta_3$ receptor, its ability to inhibit platelet

aggregation has been attributed to its function as a IIb/IIIa receptor binding inhibitor. We have now found that efficacy with respect to prevention and treatment of acute ischemic coronary syndromes is surprisingly enhanced when both the IIb/IIIa receptor and the $\alpha_v\beta_3$ receptor are blocked.

SUMMARY OF THE INVENTION

The invention is a pharmaceutical composition comprising a glycoprotein IIb/IIIa receptor antagonist and an $\alpha_v\beta_3$ receptor antagonist. The invention is also a method for reducing the risk of acute coronary ischemic syndrome in patients at risk to acute coronary ischemic syndrome comprising administering to the patient a safe and effective amount of a glycoprotein IIb/IIIa receptor antagonist and a safe and effective amount of an $\alpha_v\beta_3$ receptor antagonist.

DETAILED DESCRIPTION OF THE INVENTION

The invention is a pharmaceutical composition comprising a glycoprotein IIb/IIIa receptor antagonist and an $\alpha_v\beta_3$ receptor antagonist. In one class of these compositions, the IIb/IIIa receptor antagonist is selective for the IIb/IIIa receptor, and the $\alpha_v\beta_3$ receptor antagonist is selective for the $\alpha_v\beta_3$ receptor.

The invention is also a method for reducing the risk of acute coronary ischemic syndrome in patients at risk to acute coronary ischemic syndrome comprising administering to the patient a safe and effective amount of a glycoprotein IIb/IIIa receptor antagonist and a safe and effective amount of an $\alpha_v\beta_3$ receptor antagonist. One class of this method comprises inhibiting the binding of fibrinogen to the glycoprotein IIb/IIIa receptor and inhibiting the binding of vitronectin to the $\alpha_v\beta_3$ receptor.

The invention is also a method for reducing the risk of acute coronary ischemic syndrome in patients at risk to acute coronary ischemic syndrome comprising administering to the patient a safe and effective amount of a compound which inhibits the binding of fibrinogen to the glycoprotein IIb/IIIa receptor and which also inhibits the binding of

vitronectin to the $\alpha_v\beta_3$ receptor, wherein the compound is not monoclonal antibody 7E3.

The invention is also the use of a compound which inhibits the binding of fibrinogen to the glycoprotein IIb/IIIa receptor, or a pharmaceutically acceptable salt thereof, and a compound which inhibits the binding of vitronectin to the $\alpha_v\beta_3$ receptor, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing the risk of acute coronary ischemic syndrome in patients at risk to acute coronary ischemic syndrome.

Antagonists for the glycoprotein IIb/IIIa fibrinogen receptor have been described in United States Patents 5,470,849, 5,463,011, 5,455,243, 5,451,578, 5,446,056, 5,441,952, 5,422,249, 5,416,099, 5,405,854, 5,397,791, 5,393,760, 5,389,631, 5,380,713, 5,374,622, 5,358,956, 5,344,783, 5,340,798, 5,338,7235,334,596, 5,321,034, 5,318,899 (e.g. cyclic heptapeptides Mpr-(Acetimidyl-Lys)-Gly-Asp-Trp-Phe-Cys-NH_2, Mpr-(Acetimidyl-Lys)-Gly-Asp-Trp-Phe-Pen-NH_2, Mpr-(Phenylimidyl-Lys)-Gly-Asp-Trp-Phe-Pen-NH_2,and Mpr-(Phenylimidyl-Lys)-Gly-Asp-Trp-Phe-Cys-NH_2, wherein Mpr is mercapto propionyl), 5,312,923, 5,294,616, 5,292,756, 5,281,585 5,272,158, 5,264,420, 5,260,307, 5,239,113 (e.g. Ethyl 3-[[4-[[4-(aminoiminomethyl)phenyl]amino]-1,4-dioxobutyl]amino]-4-pentynoate), 5,227,490, 5,206,373, 4,703,036 (e.g. N-Methyl-D-phenylalanyl-N-[(1S)-1-formyl-4-guanidinobutyl]-L-prolinamide), EP 505 868 (e.g. ((1-(2-((4-(aminoiminomethyl)benzoyl)amino)-3-(4-hydroxyphenyl)-1-oxopropyl)-4-piperidinyl)oxy)-(S)-acetic acid), WO 9311152 (e.g. N-(2-(2-(((3-((aminoiminomethyl)amino)propyl)amino)-carbonyl)-1-piperidnyl)-1-(cyclohexylmethyl)-2-oxoethyl)-(R,S)-glycine), EP 333 356 and WO 9422820. They are described as useful for inhibiting fibrinogen binding and inhibiting clot formation.

Antagonists for the $\alpha_v\beta_3$ vitronectin receptor have been described in WO 9600730 and WO 9600574. These are generally described as useful for treating inflammation, cancer, atherosclerosis, restenosis, osteoporosis, hyperparathyroidism, Paget's disease, malignant hypercalcemia, metastatic osteolytic lesions, and bone loss.

Glycoprotein IIb/IIIa receptor antagonists and their pharmaceutically acceptable salts, and $\alpha_v\beta_3$ receptor antagonists and their pharmaceutically acceptable salts, are useful in the present invention. The term "pharmaceutically acceptable salts" means non-toxic salts of the compounds which include, but are not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, valerate.

Pharmaceutically effective amounts of the glycoprotein IIb/IIIa receptor antagonists and the $\alpha_v\beta_3$ receptor antagonists are suitable for use in the compositions and methods of the present invention. The term "pharmaceutically effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system or animal that is being sought by a researcher or clinician.

Compounds which are selective for the glycoprotein IIb/IIIa receptor are those having a preference (e.g. 10-fold) for binding to IIb/IIIa as compared to other receptors of the integrin family (e.g. $\alpha_v\beta_3$, $\alpha_5\beta_1$,$\alpha_v\beta_5$). Compounds which are selective for the $\alpha_v\beta_3$ receptor are those having a preference (e.g. 10-fold) for binding to $\alpha_v\beta_3$ as compared to other receptors of the integrin family (e.g. IIb/IIIa, $\alpha_5\beta_1$,$\alpha_v\beta_5$). Selectivity of these compounds can be readily determined by persons skilled in the art.

The compositions and methods of the present invention are useful in combination with procedures for treating patients with other anticoagulants (e.g. thrombin inhibitors such as heparin and Factor Xa inhibitors such as warfarin), thrombolytic agents (e.g. streptokinase and

tissue plasminogen activator), and platelet antiaggregation agents (e.g. aspirin and dipyridamole).

In accordance with the invention, glycoprotein IIb/IIIa receptor antagonists and $\alpha_v\beta_3$ receptor antagonists can be administered to the patient together in one oral composition such as a tablet or capsule or together in one intravenous solution. They may also be administered in separate dosage forms, e.g. an oral glycoprotein IIb/IIIa receptor antagonist composition with an oral $\alpha_v\beta_3$ receptor antagonist composition; an intravenous solution of a glycoprotein IIb/IIIa receptor antagonist composition with an intravenous solution of an $\alpha_v\beta_3$ receptor antagonist composition; an oral glycoprotein IIb/IIIa receptor antagonist composition with an intravenous solution of an $\alpha_v\beta_3$ receptor antagonist composition; or an intravenous solution glycoprotein IIb/IIIa receptor antagonist composition with an oral $\alpha_v\beta_3$ receptor antagonist composition. Administrations in these various ways are suitable for the present invention as long as the beneficial pharmaceutical effect of the glycoprotein IIb/IIIa receptor antagonist and $\alpha_v\beta_3$ receptor antagonist are realized by the patient at substantially the same time. Such beneficial effect is achieved when the target plasma level concentrations of each active drug are maintained at substantially the same time.

Suitable oral compositions include tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. Suitable intravenous compositions include bolus or extended infusion. Such oral and intravenous compositions are well known to those of ordinary skill in the pharmaceutical arts.

The active drugs may be administered to patients where prevention of thrombosis by inhibition of binding of fibrinogen to the platelet membrane glycoprotein complex IIb/IIIa receptor, and inhibition of binding of vitronectin to the $\alpha_v\beta_3$ receptor is desired. Such administration is useful in surgery on peripheral arteries (arterial grafts, carotid endarterectomy) and in cardiovascular surgery where manipulation of arteries and organs, and/or the interaction of platelets with artificial surfaces, leads to platelet aggregation and consumption.

The aggregated platelets may form thrombi and thromboemboli. The active drugs may be administered to these surgical patients to prevent the formation of thrombi and thromboemboli.

Other applications of the combination of active drugs include prevention of platelet thrombosis, thromboembolism and reocclusion during and after thrombolytic therapy and prevention of platelet thrombosis, thromboembolism and reocclusion after angioplasty or coronary artery bypass procedures. It may also be used to treat patients with unstable angina and prevent subsequent myocardial infarction .

The dosage regimen utilizing the active drugs is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

Oral dosages of active drug when used for the indicated effects, will range between about 0.005 mg per kg of body weight per day (mg/kg/day) to about 50 mg/kg/day and preferably 0.005-20 mg/kg/day and most preferably 0.005-10 mg/kg/day. Suitable oral tablets contain between 0.5 mg and 5 g, preferably between 0.5 mg and 2 g, most preferably between 0.5 mg and 1g, e.g. 50 mg, 150 mg, 250 mg, or 500 mg. Oral administration may be in one or divided doses of two, three, or four times daily.

Intravenously, the most preferred doses will range from about 0.5 to about 5 mg/kg/minute during a constant rate infusion, to achieve a plasma level concentration during the period of time of administration of between 0.1 ng/ml and 1 μg/ml.

The active drugs can be administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs,

syrups and the like, and consistent with convention pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, distintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn-sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch methyl cellulose, agar, bentonite, xanthan gum and the like.

Oral compositions of the active ingredient with enteric coatings may be prepared by mixing the active ingredient with an excipient to form a spheroid, and coating the spheroid with a thin polymer film. For example, the active ingredient is mixed with non-water swellable microcrystalline cellulose to form a spheroid which is then coated with a film of hydroxypropyl methyl cellulose phthalate and or a plasticizer which prevents any release of the drug in the stomach. When the composition reaches the intestine, the active ingredient is released.

The compositions may also be prepared by mixing the active ingredient with a wetting agent such as fatty acid esters, lecithin, sucrose, mannitol or sorbitol and then spheronizing or granulating the mixture into microgranules. These are then coated with a microporous membrane polymer such as Eudragit ® E30D (Rohm Pharma GmbH, Weiterstadt, Germany), hydroxypropyl methyl cellulose phthalate and other wetting

agents, plasticizers and the like. The formulations are enteric by nature and the active ingredient does not become bioavailable until the system reaches the intestine.

The compositions may also be prepared by mixing the active ingredient and an acid such as fumeric or tartaric acid which is compressed into a spherical tablet and coated with lacquers that are insoluble in gastric juices and soluble in intestinal juices. These lacquers include copolymers of acrylic acid and methacrylic acid esters. The acidic matrix prevents quick dissolution early and yet promotes the drugs' bioavailability further downstream in the digestive tract.

The compositions may also be prepared by coating a solid dosage form of the active ingredient with hydroxypropyl methyl cellulose phthalate or acidic succinyl and acetyl esters of hydroxypropyl methyl cellulose. Triethylcitrate is added as a plasticizer which aids in the binding of the coating material to the core pellet. The coating resists dissolution in the stomach but completely dissolves in the small intestine.

Suitable materials for providing enteric coatings include, for example, hydroxypropyl methyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose hexahydrophthalate, shellac, cellulose acetate, cellulose acetate phthalate, polyvinyl acetate phthalate, carboxymethyl ethyl cellulose, methacrylic acid copolymers, methacrylic ester copolymers and the like.

In general, solid dosage forms comprising the active ingredient may be coated using conventional coating techniques such as conventional pan coating techniques or column spray coating techniques.

For example, coating pans, e.g. subglobular, pear shaped or hexagonal pans, which are inclined are set to rotate at an appropriate setting sufficient to allow uncoated tablets to be exposed to spray solutions of the polymer used to form the coat. The pan is heated to a sufficient temperature to allow the coat to dry soon after contact with the outside of the tablet.

Some pans have a cylindrical shape, are rotated horizontally, and have at least some regions of the walls perforated by small holes or

slots. This design permits a one-way air flow through the pan. In other designs the flow of air is through the tablet bed and out through the perforated wall of the pan. In others the air flows from the perforated pan wall through the tablet bed into the central region, i.e., countercurrent to the coating spray direction. Still others permit either co- or counter-current air flow to suit particular products.

The coating is sprayed in one of several methods. One method relies entirely on hydraulic pressure to produce a spray when material is forced through a nozzle (airless spraying). In another method, atomization of the spray is assisted by turbulent jets of air. This method tends to produce a more easily controlled spray pattern and is therefore better for small-scale operations, although both are capable of giving the flat jet profile preferred for pan operation.

The thickness of coating required on the granules depends on the dissolution profile of the particular coating materials. The coating can contain a plasticizer and possibly other coating additives such as coloring agents, gloss producers, talc and/or magnesium stearate.

The active drugs can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Active drug may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. Active drug may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinyl-pyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxy-ethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, active drug may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals,

polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels.

Therapeutic Treatment

The compositions of the invention, and methods for administering the glycoprotein IIb/IIIa receptor antagonist and $\alpha_v\beta_3$ receptor antagonist, are useful for treating patients where inhibition of human or mammalian acute coronary ischemic syndrome is desired. They are useful in surgery on peripheral arteries (arterial grafts, carotid endaterectomy) and in cardiovascular surgery where manipulation of arteries and organs, and/or the interation of platelets with artificial surfaces, leads to platelet aggregation and potential formation of thrombi and thromboemboli. Compositions and methods of the invention may be used to prevent the formation of thrombi and thromboemboli.

The present invention is demonstrated in a study of patients with acute coronary ischemic syndromes who are undergoing early coronary revascularization with percutaneous coronary angioplasty or atherectomy. Acute coronary ischemic syndrome is associated with death and nonfatal myocardial infarction, and subsequent follow-up procedures such as coronary artery bypass grafting, repeat percutaneous intervention for acute ischemia, and insertion of a coronary endovascular stent. Because of unstable plaque with thrombus, percutaneous revascularization procedures in these patients carry with them considerable higher morbidity than procedures performed in patients with stable coronary disease. This is a similar patient population to the population studies with 7E3 as described above and where there was an increased incidence of bleeding, primarily from the site of catheterization. Patients receive either a GP IIb/IIIa receptor antagonist with an $\alpha_v\beta_3$ receptor antagonist, or placebo; all patients receive heparin (a standard PTCA regimen, weight adjusted in lighter patients) and aspirin. Heparin is discontinued after completion of the procedure and sheaths removed when the heparin-effect has dissipated. GP IIb/IIIa receptor antagonist with an $\alpha_v\beta_3$ receptor antagonist (or placebo) is continued for a total of 24 hours. Patients are evaluated at 2, 7 and 30

days, and 6 months following initiation of administration, for acute coronary ischemic syndrome.

EXAMPLE 1 (CONTROL)

gp IIb/IIIa antagonist treatment

Patients with acute coronary ischemic syndromes received coronary revascularization with angioplasty. Aspirin was administered in a dose of 325 mg at least two hours before angiopolasty, and daily thereafter. Heparin was given intravenously in an initial bolus dose of 10,000 to 12,000 units followed by incremental bolus doses of up to 3000 units at 15-minute intervals, but no more than 20,000 units was given during the procedure. The goal was to keep the activated clotting time between 300 and 350 seconds during the operation. Heparin was continued by constant infusion for at least 12 hours to maintain the activated partial-thromboplastin time at 1.5 to 2.5 times the control value. Aspirin was required at discharge in a dose of 325 mg per day.

Patients received intravenous infusion of the fibrinogen receptor gp IIb/IIIa antagonist tirofiban (2-S-(n-Butylsulfonylamino)-3[4-(piperidin-4-yl)butyloxyphenyl]propionic acid hydrochloride, described in U.S. Patent 5,292,756), in an amount sufficient to achieve a plasma level concentration of between 40-60 ng/ml, for 24 hours following angioplasty.

Patients were monitored 2, 7, and 30 days following initiation of the fibrinogen receptor gp IIb/IIIa antagonist infusion, and showed reduction in acute coronary ischemic syndrome after 2 days and 7 days, but no significant reduction at 30 days.

EXAMPLE 2

gp IIb/IIIa antagonist/$\alpha_v\beta_3$ antagonist combination treatment

Patients with acute coronary ischemic syndromes receive coronary revascularization with angioplasty. Aspirin is administered in a dose of 325 mg at least two hours before angiopolasty, and daily

thereafter. Heparin is given intravenously in an initial bolus dose of 10,000 to 12,000 units followed by incremental bolus doses of up to 3000 units at 15-minute intervals, but no more than 20,000 units is given during the procedure. The goal is to keep the activated clotting time between 300 and 350 seconds during the operation. Heparin is continued by constant infusion for at least 12 hours to maintain the activated partial-thromboplastin time at 1.5 to 2.5 times the control value. Aspirin is required at discharge in a dose of 325 mg per day.

Patients receive intravenous infusion of the fibrinogen receptor gp IIb/IIIa antagonist tirofiban (2-S-(n-Butylsulfonylamino)-3[4-(piperidin-4-yl)butyloxyphenyl]propionic acid hydrochloride, described in U.S. Patent 5,292,756), in an amount sufficient to achieve a plasma level concentration of between 40-60 ng/ml, along with intravenous infusion of the vitronectin receptor $\alpha_v\beta_3$ antagonist 7-(((6-amino-2-pyridinyl)amino)carbonyl)-4-methyl-3-oxo-2, 3, 4, 5-tetrahydro-1H-1, 4-benzodiazepine-2-acetic acid (WO 9600574), in an amount sufficient to achieve a plasma level concentration of between 40-60 ng/ml, for 24 hours following angioplasty.

Patients are monitored 2, 7, and 30 days following initiation of the fibrinogen receptor gp IIb/IIIa antagonist and vitronectin receptor $\alpha_v\beta_3$ antagonist infusions, and show significant reduction in acute coronary ischemic syndrome after 2, 7, and 30 days.

EXAMPLE 3

gp IIb/IIIa antagonist/$\alpha_v\beta_3$ antagonist combination treatment

Patients with acute coronary ischemic syndromes receive coronary revascularization with angioplasty. Aspirin is administered in a dose of 325 mg at least two hours before angiopolasty, and daily thereafter. Heparin is given intravenously in an initial bolus dose of 10,000 to 12,000 units followed by incremental bolus doses of up to 3000 units at 15-minute intervals, but no more than 20,000 units is given during the procedure. The goal is to keep the activated clotting time between 300 and 350 seconds during the operation. Heparin is continued

by constant infusion for at least 12 hours to maintain the activated partial-thromboplastin time at 1.5 to 2.5 times the control value. Aspirin is required at discharge in a dose of 325 mg per day.

Patients receive intravenous infusion of an intravenous solution comprising the fibrinogen receptor gp IIb/IIIa antagonist tirofiban (2-S-(n-Butylsulfonylamino)-3[4-(piperidin-4-yl)butyloxyphenyl]propionic acid hydrochloride, described in U.S. Patent 5,292,756) in an amount sufficient to achieve a plasma level concentration of between 40-60 ng/ml, and the vitronectin receptor $\alpha_v\beta_3$ antagonist 7-(((6-amino-2-pyridinyl)amino)carbonyl)-4-methyl-3-oxo-2, 3, 4, 5-tetrahydro-1H-1, 4-benzodiazepine-2-acetic acid (WO 9600574) in an amount sufficient to achieve a plasma level concentration of between 40-60 ng/ml, for 24 hours following angioplasty.

Patients are monitored 2, 7, and 30 days following initiation of the fibrinogen receptor gp IIb/IIIa antagonist and vitronectin receptor $\alpha_v\beta_3$ antagonist infusions, and show significant reduction in reduction in acute coronary ischemic syndrome after 2, 7, and 30 days.

EXAMPLE 4

gp IIb/IIIa antagonist/$\alpha_v\beta_3$ antagonist combination treatment

Patients with acute coronary ischemic syndromes receive coronary revascularization with angioplasty. Aspirin is administered in a dose of 325 mg at least two hours before angiopolasty, and daily thereafter. Heparin is given intravenously in an initial bolus dose of 10,000 to 12,000 units followed by incremental bolus doses of up to 3000 units at 15-minute intervals, but no more than 20,000 units is given during the procedure. The goal is to keep the activated clotting time between 300 and 350 seconds during the operation. Heparin is continued by constant infusion for at least 12 hours to maintain the activated partial-thromboplastin time at 1.5 to 2.5 times the control value. Aspirin is required at discharge in a dose of 325 mg per day.

Patients receive oral administration of 15 mg fibrinogen receptor gp IIb/IIIa antagonist 2(S)-[(p-Toluenesulfonyl)amino]-3-

[[[5,6,7,8-tetrahydro-4-oxo-5-[2-(piperidin-4-yl)ethyl]-4H-pyrazolo-[1,5-a][1,4]diazepin-2-yl]carbonyl]-amino]propionic acid, described in WO 94/18981. Patients also receive intravenous infusion of the vitronectin receptor $\alpha_v\beta_3$ antagonist 7-(((6-amino-2-pyridinyl)amino)carbonyl)-4-methyl-3-oxo-2, 3, 4, 5-tetrahydro-1H-1, 4-benzodiazepine-2-acetic acid (WO 9600574) in an amount sufficient to achieve a plasma level concentration of 40-60 ng/ml for 24 hours following angioplasty.

Patients are monitored 2, 7, and 30 days following initiation of the fibrinogen receptor gp IIb/IIIa antagonist and vitronectin receptor $\alpha_v\beta_3$ antagonist infusions, and show significant reduction in reduction in acute coronary ischemic syndrome after 2, 7, and 30 days.

EXAMPLE 5

gp IIb/IIIa antagonist/$\alpha_v\beta_3$ antagonist combination treatment

Patients with acute coronary ischemic syndromes receive coronary revascularization with angioplasty. Aspirin is administered in a dose of 325 mg at least two hours before angiopolasty, and daily thereafter. Heparin is given intravenously in an initial bolus dose of 10,000 to 12,000 units followed by incremental bolus doses of up to 3000 units at 15-minute intervals, but no more than 20,000 units is given during the procedure. The goal is to keep the activated clotting time between 300 and 350 seconds during the operation. Heparin is continued by constant infusion for at least 12 hours to maintain the activated partial-thromboplastin time at 1.5 to 2.5 times the control value. Aspirin is required at discharge in a dose of 325 mg per day.

Patients receive intravenous infusion of the fibrinogen receptor gp IIb/IIIa antagonist [3(R)-[2-Piperidin-4-yl)ethyl]-2-piperidone-1]acetyl-3(R)-methyl-β-alanine, described in U.S. Patent 5,281,585, in an amount sufficient to achieve a plasma level concentration of between 40-60 ng/ml for 24 hours following angioplasty, and oral administration of 150 mg of the vitronectin receptor $\alpha_v\beta_3$ antagonist 7-(((6-amino-2-pyridinyl)amino)carbonyl)-4-methyl-3-

oxo-2, 3, 4, 5-tetrahydro-1H-1, 4-benzodiazepine-2-acetic acid (WO 9600574).

Patients are monitored 2, 7, and 30 days following initiation of the fibrinogen receptor gp IIb/IIIa antagonist and vitronectin receptor $\alpha_v\beta_3$ antagonist infusions, and show significant reduction in acute coronary ischemic syndrome after 2, 7, and 30 days.

EXAMPLE 6

gp IIb/IIIa antagonist/$\alpha_v\beta_3$ antagonist combination treatment

Patients with acute coronary ischemic syndromes receive coronary revascularization with angioplasty. Aspirin is administered in a dose of 325 mg at least two hours before angiopolasty, and daily thereafter. Heparin is given intravenously in an initial bolus dose of 10,000 to 12,000 units followed by incremental bolus doses of up to 3000 units at 15-minute intervals, but no more than 20,000 units is given during the procedure. The goal is to keep the activated clotting time between 300 and 350 seconds during the operation. Heparin is continued by constant infusion for at least 12 hours to maintain the activated partial-thromboplastin time at 1.5 to 2.5 times the control value. Aspirin is required at discharge in a dose of 325 mg per day.

Patients receive oral administration of 15 mg of the fibrinogen receptor gp IIb/IIIa antagonist 2(S)-[(p-Toluene-sulfonyl)amino]-3-[[[5,6,7,8-tetrahydro-4-oxo-5-[2-(piperidin-4-yl)ethyl]-4H-pyrazolo-[1,5-a][1,4]diazepin-2-yl]carbonyl]-amino]propionic acid, described in WO 94/18981, and oral administration of 150 mg of the vitronectin receptor $\alpha_v\beta_3$ antagonist 7-(((6-amino-2-pyridinyl)amino)carbonyl)-4-methyl-3-oxo-2, 3, 4, 5-tetrahydro-1H-1, 4-benzodiazepine-2-acetic acid (WO 9600574) following angioplasty.

Patients are monitored 2, 7, and 30 days following initiation of the fibrinogen receptor gp IIb/IIIa antagonist and vitronectin receptor $\alpha_v\beta_3$ antagonist infusions, and show significant reduction in acute coronary ischemic syndrome after 2, 7, and 30 days.

EXAMPLE 7

gp IIb/IIIa antagonist/$\alpha_v\beta_3$ antagonist combination treatment

Patients with acute coronary ischemic syndromes receive coronary revascularization with angioplasty. Aspirin is administered in a dose of 325 mg at least two hours before angiopolasty, and daily thereafter. Heparin is given intravenously in an initial bolus dose of 10,000 to 12,000 units followed by incremental bolus doses of up to 3000 units at 15-minute intervals, but no more than 20,000 units is given during the procedure. The goal was to keep the activated clotting time between 300 and 350 seconds during the operation. Heparin is continued by constant infusion for at least 12 hours to maintain the activated partial-thromboplastin time at 1.5 to 2.5 times the control value. Aspirin is required at discharge in a dose of 325 mg per day.

Patients receive an oral tablet comprising 15 mg of the fibrinogen receptor gp IIb/IIIa antagonist 2(S)-[(p-Toluene-sulfonyl)amino]-3-[[[5,6,7,8-tetrahydro-4-oxo-5-[2-(piperidin-4-yl)ethyl]-4H-pyrazolo-[1,5-a][1,4]diazepin-2-yl]carbonyl]-amino]propionic acid, described in WO 94/18981, and 150 mg of the vitronectin receptor $\alpha_v\beta_3$ antagonist 7-(((6-amino-2-pyridinyl)amino)carbonyl)-4-methyl-3-oxo-2, 3, 4, 5-tetrahydro-1H-1, 4-benzodiazepine-2-acetic acid (WO 9600574).

Patients are monitored 2, 7, and 30 days following initiation of the fibrinogen receptor gp IIb/IIIa antagonist and vitronectin receptor $\alpha_v\beta_3$ antagonist infusions, and show significant reduction in acute coronary ischemic syndrome after 2, 7, and 30 days.

EXAMPLE 8

Tablet Preparation

Tablets containing 15 mg of the fibrinogen receptor gp IIb/IIIa antagonist 2(S)-[(p-Toluenesulfonyl)amino]-3-[[[5,6,7,8-tetrahydro-4-oxo-5-[2-(piperidin-4-yl)ethyl]-4H-pyrazolo-[1,5-a][1,4]diazepin-2-yl]carbonyl]-amino]propionic acid, described in WO

94/18981 (compound 8-1) and 150 mg of the vitronectin receptor $\alpha_v\beta_3$ antagonist 7-(((6-amino-2-pyridinyl)amino)carbonyl)-4-methyl-3-oxo-2, 3, 4, 5-tetrahydro-1H-1, 4-benzodiazepine-2-acetic acid (compounds 8-2) are prepared as illustrated below:

Tablet for doses containing 15 mg of the gp IIb/IIIa receptor antagonist and 150 mg of the $\alpha_v\beta_3$ receptor antagonist

Ingredient	mg
8-1	15.0
8-2	150.0
Microcrystalline cellulose	400.0
Modified food corn starch	17.0
Magnesium stearate	3.0

Compounds 8-1 and 8-2, cellulose, and a portion of the corn starch are mixed and granulated to 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets.

EXAMPLE 9

Intravenous formulations

An intravenous dosage form of (2-S-(n-Butylsulfonylamino)-3[4-(piperidin-4-yl)butyloxyphenyl]propionic acid hydrochloride (9-1) and 8-2 is prepared as follows:

compound 9-1	0.5-10.0 mg
compound 8-2	0.5-10.0 mg
Sodium Citrate	5-50mg
Citric Acid	1-15mg
Sodium Chloride	1-8mg
Water for Injection (USP)	q.s. to 1 L

Utilizing the above quantities, the active compound is dissolved at room temperature in a previously prepared solution of sodium chloride, citric acid, and sodium citrate in Water for Injection (USP, see page 1636 of United States Pharmacopeia/National Formulary for 1995, published by United States Pharmacopeial Convention, Inc., Rockville, Maryland, copyright 1994.

EXAMPLE 10

Intravenous formulations

A pharmaceutical composition was prepared at room temperature using compound 9-1, compound 8-2, a citrate buffer, and sodium chloride, to obtain a concentration of compound 9-1 of 0.25 mg/ml and a concentration of compound 8-2 of 0.25 mg/ml.

800 grams of water was introduced into a standard pharmaceutical mixing vessel. 0.25 grams of compound 9-1 was dissolved in the water. 2.7 grams sodium citrate and 0.16 grams citric acid were added to obtain a finished citrate concentration of 10 mM. 8 grams of sodium chloride was added. 200 grams of water was then added to achieve the desired final concentrations of ingredients. Another 800 grams of water was introduced into a second standard pharmaceutical mixing vessel. 0.25 grams of compound 8-2 was dissolved in the water. 2.7 grams sodium citrate and 0.16 grams citric acid were added to obtain a finished citrate concentration of 10 mM. 8 grams of sodium chloride was added. 200 grams of water was then added to achieve the desired final concentrations of ingredients. The finished solutions in each vessel were combined. The resulting aqueous formulation had the following concentrations:

Ingredient	Amount
compound 9-1	0.25 mg/ml
compound 8-2	0.25 mg/ml
citrate buffer	10 mM
sodium chloride	8 mg/ml

The finished concentrated formulation is stored in a standard USP Type I borosilicate glass container at 30-40 degrees C. Prior to compound administration, the concentrated formulation is diluted in a 4:1 ratio resulting in a finished concentration of 0.05 mg/ml and transferred to an infusion bag.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising a glycoprotein IIb/IIIa receptor antagonist and an $\alpha_v\beta_3$ receptor antagonist.

2. A composition of claim 1 wherein the IIb/IIIa receptor antagonist is selective for the IIb/IIIa receptor, and the $\alpha_v\beta_3$ receptor antagonist is selective for the $\alpha_v\beta_3$ receptor.

3. A composition of claim 1 wherein the glycoprotein IIb/IIIa receptor antagonist is selected from the group consisting of

Mpr-(Acetimidyl-Lys)-Gly-Asp-Trp-Phe-Cys-NH_2,

Mpr-(Acetimidyl-Lys)-Gly-Asp-Trp-Phe-Pen-NH_2,

Mpr-(Phenylimidyl-Lys)-Gly-Asp-Trp-Phe-Pen-NH_2,

Mpr-(Phenylimidyl-Lys)-Gly-Asp-Trp-Phe-Cys-NH_2,

N-Methyl-D-phenylalanyl-N-[(1S)-1-formyl-4-guanidinobutyl]-L-prolinamide,

((1-(2-((4-(aminoiminomethyl)benzoyl)amino)-3-(4-hydroxyphenyl)-1-oxopropyl)-4-piperidinyl)oxy)-(S)-acetic acid,

N-(2-(2-(((3-((aminoiminomethyl)amino)propyl)amino)carbonyl)-1-piperidnyl)-1-(cyclohexylmethyl)-2-oxoethyl)-(R,S)-glycine,

Ethyl 3-[[4-[[4-(aminoiminomethyl)phenyl]amino]-1,4-dioxobutyl]amino]-4-pentynoate

(2-S-(n-Butylsulfonylamino)-3[4-(piperidin-4-yl)butyloxyphenyl]propionic acid hydrochloride, and

2(S)-[(p-Toluenesulfonyl)amino]-3-[[[5,6,7,8-tetrahydro-4-oxo-5-[2-(piperidin-4-yl)ethyl]-4H-pyrazolo-[1,5-a][1,4]diazepin-2-yl]carbonyl]-amino]propionic acid.

4. A composition of claim 1 which is a tablet or capsule suitable for oral administration.

5. A composition of claim 1 which is an intravenous solution suitable for intravenous administration.

6. A method for reducing the risk of acute coronary ischemic syndrome in patients at risk to acute coronary ischemic syndrome comprising administering to the patient a safe and effective amount of a glycoprotein IIb/IIIa receptor antagonist and a safe and effective amount of an $\alpha_v\beta_3$ receptor antagonist.

7. A method for reducing the risk of acute coronary ischemic syndrome in patients at risk to acute coronary ischemic syndrome comprising orally administering a safe and effective amount of a glycoprotein IIb/IIIa receptor antagonist and intravenously administering a safe and effective amount of an $\alpha_v\beta_3$ receptor antagonist.

8. A method for reducing the risk of acute coronary ischemic syndrome in patients at risk to acute coronary ischemic syndrome comprising intravenously administering a safe and effective amount of a glycoprotein IIb/IIIa receptor antagonist and orally administering a safe and effective amount of an $\alpha_v\beta_3$ receptor antagonist.

9. A method for reducing the risk of acute coronary ischemic syndrome in patients at risk to acute coronary ischemic syndrome comprising inhibiting the binding of fibrinogen to the glycoprotein IIb/IIIa receptor and inhibiting the binding of vitronectin to the $\alpha_v\beta_3$ receptor.

10. A method for reducing the risk of acute coronary ischemic syndrome in patients at risk to acute coronary ischemic syndrome comprising administering to the patient a safe and effective amount of a compound which inhibits the binding of fibrinogen to the glycoprotein IIb/IIIa receptor and which also inhibits the binding of vitronectin to the $\alpha_v\beta_3$ receptor, wherein the compound is not monoclonal antibody 7E3.

11. The use of a compound which inhibits the binding of fibrinogen to the glycoprotein IIb/IIIa receptor, or a pharmaceutically acceptable salt thereof, and a compound which inhibits the binding of vitronectin to the $\alpha_v\beta_3$ receptor, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing the risk of acute coronary ischemic syndrome in patients at risk to acute coronary ischemic syndrome.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/04739

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 39/395
US CL :530/387.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/387.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	LEFKOVITS et al. Platelet glycoprotein IIb/IIIa receptor inhibitors in ischemic heart disease. Current opinion in Cardiology. 1995. Vol. 10. pages 420-426, see page 421.	1-2 and 4-8 ---------- 3
X --- Y	TOPOL et al. Prevention of cardiovascular ischemic complications with new platelet glycoprotein IIb/IIIa inhibitors. American Heart Journal. 1995. Vol. 130, Number 3, Part 2, pages 666-672, see pages 666-667.	1-2 and 4-8 ---------- 3

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
09 JULY 1997	05 AUG 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JULIE E. REEVES Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/04739

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	COLLER et al. A new murine monoclonal antibody reports an activation-dependent change in the conformation and/or microenvironment of the platelet glycoproteins IIb/IIIa complex. Journal Clinical Investigation. July 1985. Vol. 76. pages 101-108, see pages 101-102	1-2, 4-8 -------- 3
X --- Y	COLLER et al. Monoclonal antibodies to platelet glycoprotein IIb/IIIa as antithrombotic agents. Annuals of New York Academy of Sciences. 1991. Vol 614. pages 192-213, see especially pages 195-196	1-2, 4-8 --------- 3
X --- Y	COX, D. Integrins and cardiovascular disease. Expert Opinion on Investigational Drugs. May 1995. Vol 5. No. 4. pages 413-423, see especially pages 414-415	1-2, 4-8 -------- 3
X --- Y	SCHROR, K. Antiplatelet Drugs: A comparative Review. 1995. Vol 50. No. 1. pages 7-28, see especially page 21.	1-2, 4-8 -------- 3
X --- Y	HARRINGTON et al. Immediate and reversible platelet inhibtion after intravenous adminsitration of a peptide glycoprotein IIb/IIIa inhibitor during percutaneous coronary intervention. American Journal of Cardiology. 15 December 1995. Vol.76. pages 122-1227, see especially page 1222.	1-2 -------- 4-8
X --- Y	COLLER et al. Platelet vitronectin receptor expression diffferentiates Iraqi-Jewish from Arab patients with Glanzmann thrombastenia in Israel. Blood. January 1991. Vol. 77. No. 1. pages 75-83, see especially page 76.	1-2, 4-8 -------- 3
X --- Y	COOK et al. Platelet glycoprotein IIb/IIIa antagonists. Drugs of the Future. 1994. Vol 19. No. 2 . pages 135-159, see page 137.	1-2, 4-8 --------- 3
X --- Y	VERMYLEN et al. Clinical trials of primary and secondary prevention of thrombosis and restonsis. Thrombosis and Haemostasis. Vol 74. No. 1. pages 377-381, see especially page 379.	1-2, 4-8 ---------- 3
X	US 5,470,849 A (CALLAHAN et al.) 28 November 1995,col 1-2.	1-8
X	US 5,463,011 A (BROWN et al.) 31 October 1995, col 1-2.	1-8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/04739

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/04739

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

APS, MEDLINE, DIALOG
search terms: glycoprotein IIb/IIIa receptor antagonist, alpha(v)beta(3) receptor antagonist, acute coronary ischemic syndrome

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-8, drawn to a compound of a glycoprotein IIb/IIIa receptor antagonist and the alpha(v)beta(3) antagonist and their use in the method to reduce the risk of acute coronary ischemic syndrome.
Group II, claim(s) 9-10, drawn to a method of inhibiting the risk of acute coronary ischemic syndrome by adminstering compounds which inhibit the binding of fibrinogen and vitronectin.
Group III, claim(s) 11, drawn to the use of the products of claims 1-3 in the production of pharmaceutic reagents.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The species are as follows:

the 10 antagonists listed in claim 3,

Species A: Mpr-(Acetimidyl-Lys)-GLy-Asp-Trp-Phe-Cys-NH2

Species B: Mpr-(Acetimidyl-Lys)-GLy-Asp-Trp-Phe-Pen-NH2

Species C: Mpr-(Phenylimidyl-Lys)-GLy-Asp-Trp-Phe-Pen-NH2

Species D: Mpr-(Acetimidyl-Lys)-GLy-Asp-Trp-Phe-Cys-NH2

Species E: N-Methyl-D-phenylalanyl-N-[(1S)-1-formyl-4-guanidinobutyl]-L-prolinamide

Species F: ((1-(2-((4-(aminoiminomethyl)benzoyl)amino)-3-(4-hydroxyphenyl)-1-oxopropyl)-4-piperidnyl)oxy)-(S)-acetic acid

Species G: N-(2-(2-(((3-((aminoiminomethyl)amino)propyl)amino)carbonyl)-1-piperidnyl)-1-(cyclohexylmethyl)-2-oxoethyl)-R,S)-glycine

Species H: Ethyl 3-[[4-[[4-(aminoiminomethyl)phenyl]amino]-1,4-dioxobutyl]amino]-4-pentynoate

Species I: (2-S-(n-Butylsulfonylamino)-3[4-(piperidin-4-yl)butyloxyphenyl]propionic acid hydrochloride and

Species J: 2(S)-[(p-Tolunesulfonyl)amino]-3-[[[5,6,7,8-tetrahydro-4-oxo-5-[2-piperidin-4yl)ethyl]4H-pyrazolo-[1,5-a][1,4]diazepin-2-yl]carbonyl]-amino]propionic acid

Each antagonist is deemed to be a different species.

The inventions listed as Groups I-III do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Group I contains the special technical feature of a method of reducing the risk of acute coronary ischemia by administering the

antagonist compounds of claims 1-3 that is not necessary for the practice of Groups II and III. Group II contains the special technical feature of administering fibrinogen and vitronectin inhibitors that are not necessary for the practice of Groups I and III. Group III contains the special technical feature of making pharmaceutical compounds that are not needed for the practice of Groups I and II.

The ten species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: the ten antagonists recited in claim 3 each have varying structure and functional properties that do not relate to a single inventive concept. If no species is elected, then the first species, Species A, will be searched.